May 24, 2002

Bruce K. Bernard, Ph.D.
President, SRA International, Inc.
1920 L Street, NW
Suite 420
Washington, DC 20036

Dear Dr. Bernard:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the N-(methyl)-Acrylamides category, posted on the ChemRTK HPV Challenge Program Web site on October 15, 2001. I commend the NMA/NBMA Association for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its HPV Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the attached Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the NMA/NBMA Association advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the HPV Challenge Program Web site "Submit Technical Questions" button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
A. Abramson
C. Auer
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
N-(Methyl)-Acrylamides

SUMMARY OF EPA COMMENTS

SRA International, Inc., on behalf of the NMA/NBMA Association, submitted a test plan and robust summaries to EPA for the N-(methyl)-acrylamides category dated September 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on October 15, 2001. The N-(methyl)-acrylamides category includes N-(hydroxymethyl) acrylamide (NMA) (CAS No. 924-42-5) and N-(butoxymethyl) acrylamide (NBMA) (CAS No. 1852-16-0).

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. The proposed category includes NMA and NBMA, and the submitter proposed that these can be grouped together with the structural analog acrylamide (AMD). However, the submitter needs to discuss similarities in metabolism, distribution, and biological activities (including modes of action) of AMD, NMA, and NBMA that are likely to provide important support for grouping these chemicals together and for using AMD as an analog for NMA and NBMA.

2. Physicochemical and Environmental Fate Data. (a) The submitter needs to correct the reported water solubility estimate for NBMA. (b) The submitter needs to address inconsistent statements regarding biodegradation of NMA. (c) The submitter needs to provide input values for transport and distribution (fugacity) estimations.

3. Health Endpoints. (a) The submitter proposed that no additional testing is needed for NMA and NBMA, because adequate data for AMD are available that could be used to address the health effects endpoints for NMA and NBMA. However, as stated above, the submitter needs to provide a stronger justification for using AMD as a structural analog. (b) Until this information is provided, EPA considers the developmental toxicity endpoint unaddressed and additional testing may be necessary.

4. Ecotoxicity. The submitter considered the existing data for AMD, NMA, and NBMA adequate to address ecotoxicity endpoints for NMA and NBMA. However, given the absence of aquatic invertebrate and algae testing for NMA and NBMA, and the failure of the submitter to demonstrate the relevance of the AMD data, EPA recommends that additional acute toxicity testing is necessary on aquatic invertebrate and algae for at least NBMA.

EPA requests that the Submitter advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON N-(METHYL)-ACRYLAMIDES CATEGORY CHALLENGE SUBMISSION

Category Definition

The N-(methyl)-acrylamides category includes two chemicals: N-(hydroxymethyl)-acrylamide (NMA, CAS No. 924-42-5) and N-(butoxymethyl)-acrylamide (NBMA, (CAS No. 1852-16-0).

Category Justification

The submitter did not name acrylamide (AMD) itself as a member of the category, but proposed that AMD, NMA, and NBMA can be grouped together because of their "close structural similarities" (all have the acrylamide moiety) and "relatively minor" structural differences (variation in the N-substituent: -H for AMD; -CH_2OH for NMA; and -$CH_2OCH_2CH_2CH_2CH_3$ for NBMA).

The submitter did not discuss similarities in metabolism and distribution, biological activities, and chemical reactivities among AMD, NMA, and NBMA that are likely to provide important support for grouping these chemicals, and using AMD as an analog for NMA and NBMA. The revised justification should clearly discuss the evidence supporting the hypotheses that (1) AMD is a good toxicological analog for NMA and NBMA, and (2) AMD is equally toxic or more toxic than NMA and NBMA. Issues that need to be addressed in this justification include:

1. For ecotoxicity: The only ecotoxicity endpoint for which there are data for all three chemicals are static 96-hour LC_{50} values in rainbow trout. The submitter claimed that the apparent potency of NBMA and AMD are similar in this assay, but the LC_{50} values indicate that NBMA is more potent than AMD. This does not support the submitter's conclusion that "the use of data from AMD to substitute for missing data for NMA or NBMA provides a good but likely conservative estimate."

2. For chemical reactivity and metabolism: The submitter needs to provide discussion on whether the acrylamide moiety is responsible for AMD-induced neuropathies, lesions in male reproductive organs, genotoxic actions, and/or carcinogenicity, or whether metabolites are responsible for these effects. The submitter also needs to discuss the known or postulated mode of action of NMA or NBMA in producing similar effects as AMD to support the contention that AMD can be used as a analog for this category. While the submitter stated that, in dilute aqueous solutions, NMA and NBMA undergo slow hydrolysis to yield AMD, the submitter did not cite supporting data or references or discuss whether this property is likely to result in similar environmental or biological behavior.

Test Plan

The submitter concluded that no further testing is needed for NMA and NBMA because there are adequate data for all endpoints on AMD, and proposed that AMD data be used to address endpoints for NMA and NBMA. As discussed above, the submitter needs to present a stronger justification for using AMD as an analog for NMA and NBMA. Discussed below, are several SIDS-level endpoints for which there are no data or inadequate data for NMA and NBMA (ecotoxicity tests for NMA and NBMA, repeated dose toxicity tests for NBMA, and developmental toxicity tests for NMA and NBMA).

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient).

Adequate existing data are available for these endpoints.

Water Solubility. The reported water solubility value for NBMA of 0.00012 mg/L (1.2×10^{-4} mg/L) at 25° C (Test Plan p. 7; Robust Summaries, p. 4/14) is incorrect. The actual EPIWIN value is 1.2×10^{4} mg/L (12 g/L).

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

Adequate existing data are available for these endpoints.

Biodegradation. The submitter needs to address the following inconsistent statements regarding biodegradation: The submitter indicates on page 10 of the Test Plan, that based on EPIWIN modeling, all three compounds will biodegrade rapidly in water. However in the Robust Summary it indicates that NMA is not readily biodegradable (51.9 % after 28 days) based on OECD guideline 301D (page 6/33).

Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

AMD is a well characterized and data-rich chemical. AMD data could be used to address health effects endpoints for NMA and NBMA provided that the submitter presents a discussion on the similarities among the chemicals' toxicokinetics properties. The following comments are made assuming that the submitter will provide this information.

Acute Toxicity. Although the majority of the summarized studies on NMA, and NBMA appear inadequate on an individual basis, the combined acute oral toxicity data for AMD, NMA, and NBMA are adequate to address this endpoint.

Repeated Dose Toxicity. Adequate repeated dose toxicity studies are available for NMA (and AMD). EPA considers the repeated-dose toxicity study of NBMA (Huntingdon Research Center, 1976) inadequate because it did not include histopathological and clinical pathology examinations. The submitter-assigned reliability code of 1 for this summary is inappropriate. EPA considers that this endpoint has been addressed for the purposes of the HPV Challenge Program by reading across from the adequate data for NMA (and AMD).

Genetic Toxicity. Available genetic toxicity data for NMA, NBMA, (and AMD) are adequate to address this endpoint. However, the submitter needs to address numerous deficiencies as detailed below.

Reproductive Toxicity. Adequate data are available for NMA (and AMD). EPA considers that this endpoint has been addressed for the purposes of HPV Challenge Program by reading across from the adequate data for NMA (and AMD).

Developmental Toxicity. No data were submitted for NMA or NBMA. Two of the four robust summaries (Sprague-Dawley rats and Swiss mice (Field et al., 1990)) on AMD are adequate. However, until the submitter provides a more convincing argument for using AMD data to substitute for the missing data for NMA and NBMA, EPA considers that this endpoint has not been adequately addressed and that there may be a need for additional developmental toxicity testing.

Carcinogenicity. Five robust summaries (3 AMD and 2 NMA) were submitted for carcinogenicity studies. Although this is not an HPV/SIDS endpoint, robust summaries of the non-neoplastic findings from these studies would strengthen the repeated dose toxicity section.

Ecotoxicity

The submitter provided acute toxicity studies in fish for the two category chemicals (NMA and NBMA). The submitter also provided acute studies in fish, invertebrates, and algae for AMD, although the relevance of these tests to NMA and NBMA was not established. The submitter's test plan calls for no additional ecotoxicity testing.

Fish. The submitter provided data on the acute toxicity of NMA and NBMA to fish. EPA considers these data adequate to address the acute toxicity endpoint for these chemicals.

Invertebrates. No data were submitted on the toxicity of NMA or NBMA to aquatic invertebrates. Instead, the submitter provided data on the acute and chronic toxicity of AMD to aquatic invertebrates. The test plan calls for no testing of aquatic invertebrates for acute toxicity of NMA or NBMA. However, the relevance of the data for AMD to NMA and NBMA was not established. Therefore, the submitter's test plan for toxicity to aquatic invertebrates is not supported. Because NBMA is more toxic in fish than NMA (and AMD), EPA recommends that the submitter conduct additional testing on NBMA.

Algae. No data were submitted on the toxicity of NMA or NBMA to algae. Instead, the submitter provided data on the toxicity of AMD to algae. The test plan calls for no testing of algae for acute toxicity of NMA or NBMA. However, the relevance of the data for AMD to NMA and NBMA was not established. Therefore, the submitter's test plan for algal toxicity is not supported. Because NBMA is more toxic in fish than NMA (and AMD), EPA recommends that the submitter conduct additional testing on NBMA.

Specific Comments on the Robust Summaries

Environmental Fate

Fugacity.

The submitter needs to provide the assumptions and data inputs to the model.

Health Effects

Acute Toxicity.

NMA. Data submitted for two oral studies conducted in rats and mice (Battelle, 1981a, 1981b) appear to be adequate for characterization of the endpoint. However, the submitter should independently verify the LD_{50} values of 400 mg/kg obtained from these studies. Mortality at the 400 mg/kg dose was 7/10 and 6/10 for rats and mice, respectively, and the method for LD_{50} calculation was not reported. The remaining summaries were inadequate based on deficiencies in study design (use of too few animals or doses or concentrations; post-treatment observation period of less than 14 days) or reporting (sex or strain of animals; clinical signs; mortality data; method of LD_{50} calculation; etc.).

NBMA. One out of four robust summaries (Carpenter, 1971) may be marginally adequate if information can be provided on the fasting status of orally dosed animals; administered dose in mg/kg; period of post-treatment observation; and method of LD_{50} calculation. The other studies are inadequate based on deficiencies in study design, methods, and reporting similar to those noted above.

Genetic Toxicity.

Many of the summaries submitted for genetic toxicity studies on NMA, NBMA , (and AMD) lack sufficient detail on experimental design, methods, and results. Missing information commonly includes source/type of metabolic activation system; number of concentrations tested; number of replicates tested at each concentration; evidence for cytotoxicity; use and identity of positive controls; criteria for a positive response; whether statistical analysis was performed; number of cells evaluated (chromosomal aberration endpoint); summary data for results; etc. The submitter needs to obtain and incorporate this information from the original study reports.

Followup Activity

EPA requests that the Submitter advise the Agency within 90 days of any modifications to its submission.